

SUPPLEMENTARY MATERIAL

Table S1. Demographic features of 30 genetically unsolved CVID patients with (CSR-D) or without (Non CSR-D) class switch recombination defect

ID	Gender	Cons.	Age at Evaluation (year)	Age at Onset (year)	Delay in Diagnosis (year)	Clinical Phenotype	Major Clinical Manifestations
CSR-D1	M	-	49	0.5	40	IO	Eosinophilic Granulomatosis in Right Knee
CSR-D2	M	+	43	2	28	CE	Chronic Enteropathy
CSR-D3	M	+	36	10	14	IO	-
CSR-D4	F	-	30	7	20	IO	-
CSR-D5	M	+	18	0.5	9	IO	-
Non CSR-D1	M	+	45	0	24	CE, AI (overlap syndrome)	Chronic Enteropathy Psoriasis
Non CSR-D2	M	-	43	0.5	34	CE	Chronic Enteropathy
Non CSR-D3	F	-	41	8	20	IO	-
Non CSR-D4	M	-	41	31	4	CE, LP (overlap syndrome)	Splenomegaly Chronic Bronchiectasis Chronic Enteropathy
Non CSR-D5	F	-	39	26	2	CE	Chronic Enteropathy
Non CSR-D6	M	+	37	6	13	IO	-
Non CSR-D7	M	+	37	17	4	AI	Rheumatoid Arthritis Bronchiectasis
Non CSR-D8	F	-	33	7	12	IO	-
Non CSR-D9	F	-	32	5	11	IO	Chronic Bronchiectasis
Non CSR-D10	M	+	31	5	9	AI, LP (overlap syndrome)	Chronic Lymphocytic Hyperplasia Bronchiectasis Hypothyroidism
Non CSR-D11	M	-	28	6	16	IO	Bronchiectasis
Non CSR-D12	M	+	24	4	7	IO	Hepatitis (C)
Non CSR-D13	F	-	24	4	17	CE	Bronchiectasis Chronic Enteropathy
Non CSR-D14	M	-	23	10	2	AI	Rheumatoid Arthritis
Non CSR-D15	F	-	21	19	0	IO	Dermatitis
Non CSR-D16	F	+	21	10	0.2	IO	-
Non CSR-D17	M	-	20	11	3	IO	-
Non CSR-D18	M	-	16	7	0.5	IO	-
Non CSR-D19	F	+	16	4	5	IO	Dermatophytosis
Non CSR-D20	M	+	12	0.5	9	IO	-
Non CSR-D21	M	+	10	3.5	2.5	IO	Bronchiectasis
Non CSR-D22	M	-	6	0.5	3	IO	-
Non CSR-D23	M	+	16	0.5	6	CE, LP (overlap syndrome)	Chronic Enteropathy Lymphadenopathy

Non CSR-D24	F	+	8	1.5	0	LP	Nodular Lymphoid Hyperplasia
Non CSR-D25	M	-	32	2.5	26	CE	Chronic Enteropathy Celiac Disease Bronchiectasis

*HC: Healthy Control, IO: Infection only, AI: Autoimmunity, CE: Chronic Enteropathy, LP: Lymphoproliferation
M; Male, F; Female. Cons.; Consanguinity Overlap syndrome; Patients may have more than one complication.*

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Table S2. Study population demographic data and characteristics

Parameters	Total (N=30)	CSR-D (N=5)	Non CSR-D (N=25)	<i>p</i> -value
Gender (Male/Female)	20/10	4/1	16/9	0.505
Consanguinity [n (%)]	14(47)	3(60)	11(44)	0.529
Age (years) at evaluation (Mean \pm SEM)	28 \pm 2	36 \pm 5	26 \pm 2	0.121
Age (years) at onset (Mean \pm SEM)	7 \pm 1.4	4 \pm 2	7.6 \pm 1.6	0.342
Delayed Diagnosis (years) (Mean \pm SEM)	11 \pm 2	22 \pm 5	9 \pm 2	0.01
Bronchiectasis [n (%)]	8(27)	0(0)	8(32)	0.003
Otitis [n (%)]	16(53)	4(80)	12(48)	0.202
Pneumonia [n (%)]	25(83)	5(100)	20(80)	0.022
Hospitalization [n (%)]	27(90)	5(100)	22(88)	0.432
IO [n (%)]	18(60)	4(80)	14(56)	0.324
Non IO [n (%)]	12(40)	1(20)	11(44)	0.324
AI [n (%)]	3(10)	0(0)	3(27)	0.432
CE [n (%)]	8(27)	1(100)	7(64)	0.723
LP [n (%)]	1(3)	0(0)	1(9)	0.663

CSR-D: Patients with class switch recombination defects

Non CSR-D: Patients without class switch recombination defects

SEM: standard error of the mean

IO: Infection only, AI: Autoimmunity, CE: Chronic Enteropathy, LP: Lymphoproliferation

Table S3. Lymphocyte subsets in CSR-D and Non CSR-D COVID patients in comparison to their age- and sex-matched healthy controls

Cell subsets ^a	Surface markers	HC	CSR-D	HC	Non CSR-D
		(n=5)	(n=5)	(n=25)	(n=25)
B cells	CD19 ⁺	10±2	6.2±1.6	7 ±0.6	3.9±0.7**
Helper T cells	CD3 ⁺ CD4 ⁺	43.2±3	31±3.6	43.1±1.6	34±2**
Cytotoxic T cells	CD3 ⁺ CD8 ⁺	24±3	30±4.5	24±1.5	34.4±2.8**
B cell subsets					
Naive	IgD ⁺ IgM ⁺ CD27 ⁻	5.8±1	5.1±1.4	4.2±0.5	2.9±0.6
MZB	IgD ⁺ IgM ⁺⁺ CD27 ⁺	0.5±0.15	0.15±0.06	0.28±0.04	0.11±0.03**
SMB	IgD ⁻ IgM ⁻ CD27 ⁺	0.8±0.14	0.1±0.03*	0.48±0.05	0.1±0.01***
IgM only MB	IgD ⁻ IgM ⁺⁺ CD27 ⁺	0.12±0.02	0.008±0.004**	0.13±0.03	0.01±0.003***
CD21 ^{low} B cells	CD21 ^{-/lo} CD38 ^{-/lo} IgM ^{hi}	0.14±0.03	0.4±0.17	0.12±0.03	0.23±0.06
Transitional	CD21 ⁺ CD38 ⁺⁺ IgM ^{+/+++}	0.29±0.13	0.51±0.3	0.24±0.07	0.24±0.09
Plasmablast	CD21 ^{-/lo} CD38 ^{+/+++} IgM ⁻	0.07±0.02	0.02±0.01*	0.1±0.02	0.02±0.005***
CD4⁺ T cell subsets					
Naive	CD45RA ⁺ CCR7 ⁺	18±3.9	12±5.8	21±1.5	9.6 ±1.9***
Central Memory	CD45RA ⁻ CCR7 ⁺	13±0.9	9±1.4	11±0.8	8.2±1**
Effector Memory	CD45RA ⁻ CCR7 ⁻	11±2.3	8±2.8	7.2±0.6	9.8±1.2
T _{EMRA}	CD45RA ⁺ CCR7 ⁻	0.6±0.12	1.5±0.5	1.5±0.6	1.6±0.5
T helper1	IFN γ ⁺ IL17 ⁻	4.6±0.9	3.3±1.3	5.4±0.6	5.4±0.7
T helper2	IL4 ⁺ IFN γ ⁻ IL17 ⁻	0.47±0.18	0.5±0.09	0.4±0.09	0.55±0.1
T helper17	IFN γ ⁻ IL17 ⁺	0.5±0.14	0.42±0.06	0.5±0.06	0.57±0.1
Treg	CD25 ⁺ FOXP3 ⁺ CD127 ^{-/lo}	0.6±0.2	0.36±0.11	0.72±0.1	0.27±0.05***
CD8⁺ T cell subsets					
Naive	CD45RA ⁺ CCR7 ⁺	10±2.5	6±2.3	8.7±0.7	6.4±0.9*
Central Memory	CD45RA ⁻ CCR7 ⁺	1.2±0.2	1.4±0.5	1.4±0.2	2±0.6
Effector Memory	CD45RA ⁻ CCR7 ⁻	7±2	12±5.2	5.1±0.5	10±1.5*
T _{EMRA}	CD45RA ⁺ CCR7 ⁻	5±1.4	9.5±2	7±0.9	14±1.9*
Activated CD8 ⁺ T cell	HLADR ⁺ CD38 ⁺	1.7±0.26	7.4±2.4	1.6±0.3	9.2±1.1***
Cytotoxic CD8 ⁺ T cell	Granzyme B ⁺	16±5.2	23±8	6.6±0.7	27±3.2***

^a: of lymphocyte population.

All values are presented as Mean ± SEM of percentage (%).

HC: healthy control; MZB: marginal zone B cells; SMB: switched memory B cells; IgM only MB: IgM only memory B cells; T_{EMRA}: terminally differentiated effector memory; Treg: regulatory T cells

P-values show the significant differences of lymphocyte subsets in either CSR-D or Non CSR-D group compared with its matched HC.

P values less than 0.05 are regarded as significant.

*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$

Table S4. Number and percentage of CSR-D and Non CSR-D COVID patients with abnormality in B and T cell subsets based on the calculated cut-off values

Cell subsets ^a	CSR-D (n=5)	Non CSR-D (n=25)	Cut-off value	Sensitivity	Specificity	Area (CI)	p value
	Number (%)	Number (%)					
B cells ↓	2 (40)	20 (80)	5.3	73.3	73.3	0.773 (0.652-0.894)	0.122
Helper T cells ↓	1 (20)	7 (28)	26.5	73.3	70	0.219 (0.102-0.337)	0.561
Cytotoxic T cells ↑	2 (40)	10 (40)	39.5	70	70	0.736 (0.606-0.866)	0.487
B cell subsets							
Naive ↓	2 (40)	16 (64)	2.9	60	66.7	0.662 (0.522-0.802)	0.872
MZB ↓	2 (40)	21 (84)	0.175	80	73.3	0.811 (0.701-0.921)	0.589
SMB ↓	5 (100)	24 (69)	0.317	100	83.3	0.953 (0.904-1)	1
IgM only MB ↓	5 (100)	23 (92)	0.021	93.3	80	0.911 (0.839-0.982)	0.957
CD21 ^{low} B cells ↑	4 (80)	12 (48)	0.1	53.3	60	0.561 (0.411-0.71)	0.208
Transitional ↑	3 (60)	9 (36)	0.136	40	43.3	0.387 (0.237-0.536)	0.275
Plasmablast ↓	4 (80)	22 (88)	0.04	86.7	73.3	0.862 (0.769-0.956)	0.957
CD4⁺ T cell subsets							
Naive ↓	4 (80)	22 (88)	14.04	86.7	80	0.827 (0.710-0.944)	0.872
Central Memory ↓	3 (60)	16 (64)	9.72	63.3	76.7	0.734 (0.608-0.861)	0.681
Effector Memory ↑	2 (40)	17 (68)	7.27	63.3	50	0.588 (0.438-0.737)	0.516
T _{EMRA} ↑	5 (100)	14 (56)	0.593	63.3	53.3	0.536 (0.386-0.686)	0.9
T helper1 ↓	4 (80)	14 (56)	4.12	63.3	66.7	0.584 (0.434-0.735)	0.208
T helper2 ↑	3 (60)	16 (64)	0.356	63.3	60	0.613 (0.469-0.758)	0.787
T helper17 ↑	2 (40)	13 (52)	0.416	50	43.3	0.219 (0.102-0.337)	0.829
Treg ↓	4 (80)	18 (72)	0.330	73.3	73.3	0.773 (0.654-0.893)	0.122
CD8⁺ T cell subsets							
Naive ↓	4 (80)	16 (64)	6.61	66.7	66.7	0.710 (0.577-0.843)	0.934
Central Memory ↑	3 (60)	11 (44)	0.887	53.3	56.7	0.542 (0.391-0.694)	0.872

Effector Memory↑	3 (60)	16 (64)	8.46	63.3	90	0.667 (0.512-0.821)	0.705
T _{EMRA} ↑	4 (80)	17 (68)	7.71	70	73.3	0.697 (0.555-0.838)	0.171
Activated CD8 ⁺ T cell↑	4 (80)	22 (88)	2.54	86.7	83.3	0.904 (0.821-0.986)	0.539
Cytotoxic CD8 ⁺ T cell↑	4 (80)	22 (88)	9.14	86.7	70	0.849 (0.746-0.952)	0.709

^a: of lymphocyte population.

P-values for lymphocyte subsets are obtained by statistical analysis to compare CSR-D group with Non CSR-D group.

The abnormality in each subset is shown as increase (↑) or decrease (↓) based on the related cut-off value.

HC: healthy control; MZB: marginal zone B cells; SMB: switched memory B cells; IgM only MB: IgM only memory B cells;

T_{EMRA}: terminally differentiated effector memory; Treg: regulatory T cells.